ORIGINAL ARTICLE

Efficacy and safety of livwin (polyherbal formulation) in patients with acute viral hepatitis: A randomized double-blind placebo-controlled clinical trial

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ABSTRACT

Objectives: The study was planned to evaluate the efficacy and safety of Livwin (polyherbal formulation) in acute viral hepatitis. **Materials and Methods:** In this study, there were 29 patients in each group, receiving either Livwin (containing *Ashwagandha, Arjuna, Bhumyamalaki, Daruharidra, Guduchi, Kutki and Punarnava*) or placebo capsules containing lactose powder (500 mg). Both drugs were given orally two capsules two times a day for eight weeks followed by treatment free period of four weeks. Recovery of patients was assessed by noting symptomatic recovery and by measuring levels of serum bilirubin, serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), alkaline phosphatase at baseline, 2, 4, 8 and 12 weeks. **Results:** Significant earlier recovery of weakness was observed with Livwin as compared to placebo at 2, 4 and 8 weeks. Serum bilirubin and ALT was observed in normal range in significantly more number of patients with Livwin treatment as compared to placebo at 2, 4 and 8 weeks. AST was observed in normal range in significantly more number of patients with Livwin treatment as compared to placebo at 2 and 4 weeks. **Conclusions:** Livwin is found effective in uncomplicated patients of acute viral hepatitis. Epigastric pain and diarrhea were reported with Livwin treatment.

Key words: Acute hepatitis, *Phyllanthus niruri* linn, *Tinospora cordifolia* (willd.) miers

INTRODUCTION

Viral hepatitis is a global public health problem occurring endemically and sporadically throughout the world. There have been numerous outbreaks reported from various parts of India.[1]

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The therapy for viral hepatitis assumes immense importance as death from this disease is much more common in India due to poor standard of nutrition than it is in the West, though natural cure may occur with or without residual liver cell damage.[2] Hence, problem of therapy for viral hepatitis demands an ideal drug with essential requisite of quicker recovery and convalescence without residual liver disease. At present, there are no established drugs for hepatitis A, hepatitis E and hepatitis G.[3]

Polyherbal formulations[4,5] have been reported to reduce mean period required for biochemical recovery (LFT) after hepatitis infection and there were no reported or observed significant adverse events.

With this background, the present study was planned to evaluate the efficacy and safety of Livwin in comparison to placebo in patients of acute viral hepatitis.

MATERIALS AND METHODS

This was a prospective, double blind, randomized, placebo

controlled, clinical trial. Sixty patients of uncomplicated acute viral hepatitis patients enrolled for this study. One patient from each group dropped out as they did not follow up. Patients were recruited from the Medicine OPD of Indira Gandhi Government Medical College, Nagpur. This study was approved by Institutional Ethics Committee of Indira Gandhi Government Medical College, Nagpur. A written informed consent was taken from each patient.

Inclusion criteria

Patients with diagnosis of symptomatic acute viral hepatitis (less than 6 months).[3]

Exclusion criteria

Age <15 years, pregnancy, patient of viral hepatitis associated with complications, hepatocellular failure, hepatic encephalopathy, portal hypertension/ascitis, patient with chronic hepatitis (more than 6 months), bleeding tendencies, sickle cell disease/ thalassemia major (hemolytic anemia), obstructive jaundice, alcoholic hepatitis, drug-induced hepatitis.

Material

Livwin is polyherbal formulation that contains extracts of seven medicinal plants as follows: Arjuna (*Terminalia arjuna* W and A) – 100 mg, Ashwagandha (*Withania somnifera* Dunal) – 100 mg, Bhumyamalaki (*Phyllanthus niruri* Linn) – 100 mg, Daruharidra (*Berberis aristata* DC) – 50 mg, Guduchi (*Tinospora cordifolia* (Willd.) Miers) – 75 mg, Kutki (*Picrorhiza kurroa* Royle ex Benn.) – 50 mg, Punarnava *(Boerhaavia diffusa Linn)* – 50 mg. Placebo capsule was containing lactose powder 500 mg.

Both Livwin and placebo were given orally, two capsules two times a day for eight weeks followed by drug treatment free period of four weeks. Baidhyanath Research Foundation, Nagpur provided the formulation in the form of inert gelatin capsule of same color, which contained either drug or placebo. The capsules were packaged in container that was labeled as drug code either A or B. Codes were given as Drug A for Livwin and Drug B for Placebo. Both the investigator and patient were unaware of the treatment. The codes were broken only on completion of the study as no patient developed serious adverse reactions during the study period. The diagnosis of acute viral hepatitis was made by physician based on clinical criteria such as jaundice, yellow urine, fever, nausea, vomiting, weakness, tender hepatomegaly and biochemical criteria like raised serum bilirubin, AST (serum aspartate aminotransferase), ALT (serum alanine aminotransferase) and serum alkaline phosphatase.[6] Serological investigation was done for only for Hepatitis B, other serological markers for other viral hepatitis were not done due to high cost of investigations.

Efficacy of Livwin in acute viral hepatitis was evaluated by recovery of weakness and by measuring serum bilirubin and activity of enzymes AST, ALT and serum alkaline phosphatase at baseline, 2, 4, 8 and 12 weeks. Serum bilirubin[7] was quantitatively estimated by semi-autoanalyser, TRANSASIA, ERBA, CHEM-5- PLUS. ALT,[8] AST[9] and serum alkaline phosphatase[6] were quantitatively determined by using autoanalyser, AUTOLAB AMS, Analyzer Medical System. Values of serum bilirubin 0.10–1.20 mg/dl, ALT 10–40 IU/L, AST 5–40 IU/L and alkaline phosphatase 32–92 IU/L were considered as normal range with these methods.

No other therapy was given to patients during the study period. Vigilant follow-up of patients for adverse drug reactions was done and recorded in the case report form.

Statistical analysis of data

At the level of significance $\alpha = 5\%$ and power 90%, the sample size of 29 for each group was calculated by statistician using pilot study data of 10 patients in each group. Randomization of 58 patients was done with the help of randomization number table. Fisher's Exact Test was used for the statistical comparison of recovery of the number of patients for weakness, serum bilirubin, AST, ALT and serum alkaline phosphatase at 2, 4, 8 and 12 weeks. $P<0.05$ was considered as statistically significant.

Results

Both the groups were comparable in age, sex and duration of illness [Table 1] There was significant clinical recovery of fever, weakness, icterus and tender and enlarged liver at 2 weeks with Livwin as compared to placebo [Table 2]. Weakness improvement was observed in significantly more number of patients with Livwin treatment as compared to placebo at 2, 4 and 8 weeks [Table 2]. Serum bilirubin was observed in normal range in significantly more number of patients with Livwin treatment as compared to placebo at 2, 4 and 8 weeks. AST was observed in normal range in significantly more number of patients with Livwin treatment as compared to placebo at 2 and 4 weeks. ALT was observed in normal range in significantly more number of patients with Livwin treatment as compared to placebo at 2, 4 and 8 weeks. Serum alkaline phosphatase was observed in normal range in more number of patients with Livwin treatment as compared to placebo at 2 and 4 weeks, but no significant difference was observed [Table 3].

Table 1: Demographic characteristics of patients

Group	Livwin	Placebo
Number of patients	29	29
Age (yrs)	29.93 ± 2.70 (Range 16–73)	33.37 ± 2.43 (Range 15–65)
Sex		
Male (No.)	22	25
Female (No.)	7	4
History: duration of illness (days)	11.55 ± 0.95	10.41 ± 1.01

Values are given as mean ± S.E.M. where appropriate.

Table 2: No / (%) of patients recovered of fever, weakness, icterus and tender and enlarged liver at 2, 4, 8 and 12 weeks with livwin and placebo treatment

Symptom/ Sign	Group	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Fever	Livwin	0 (0)	29 (100)***	29 (100)	29 (100)	29 (100)
	Placebo	0 (0)	11 (37.93)	28 (96.55)	28 (96.55)	29 (100)
Weakness	Livwin	0 (0)	22 (75.86)***	29 (100)***	29 (100)*	29 (100)
	Placebo	0 (0)	1 (3.44)	5 (17.24)	25 (86.20)	27 (93)
Icterus	Livwin	0 (0)	24 (82.75)***	28 (96.55)***	29 (100)***	29 (100)
	Placebo	0 (0)	1 (3.44)	14 (48.27)	20(68.96)	29 (100)
Tender and Enlarged Liver	Livwin	3 (10)	24 (83)**	29 (100)**	29 (100)	29 (100)
	Placebo	4 (14)	14 (48)	23 (79)	28 (96.55)	29 (100)

*$P < 0.05$, **$P < 0.01$,*** $P < 0.001$., $n = 29$,

Table 3: No / % showing patients who had achieved levels of serum bilirubin, AST, ALT, Serum alkaline phosphates in normal range

Parameter	Drugs	Baseline	2 weeks	4 weeks	8 weeks	12 weeks
Serum Bilirubin < 1.2 mg/dl	Livwin	0 (0)	11 (37.93)**	18 (62.06)*	28 (96.55)***	26 (89.66)
	Placebo	0 (0)	2 (6.90)	10 (34.48)	17 (58.62)	23 (79.31)
AST < 40IU / Liter	Livwin	0 (0)	8 (27.59)	14 (48.28)	19 (65.52)	24 (82.76)
	Placebo	0 (0)	0 (0)	3 (10.34)	17(58.62)	24(82.76)
ALT < 40IU / Liter	Livwin	0 (0)	8 (27.59)**	26 (89.66)***	29 (100)***	29 (100)
	Placebo	0 (0)	0 (0)	5 (17.24)	15 (51.72)	27 (93.10)
Serum Alkaline Phosphatase < 92 IU/Liter	Livwin	2 (6.90)	11 (37.93)	20 (68.97)	22 (75.86)	24 (82.76)
	Placebo	2 (6.90)	7 (24.13)	14 (48.28)	23 (79.31)	24 (82.76)

*$P<0.05$, **$P<0.01$, ***$P<0.001$

Table 4: Adverse events reported during study period in livwin and placebo

Adverse events	Livwin	Placebo
Epigastric pain	2 (6.89%)	2 (6.89%)
Diarrhea	1 (3.44%)	_

n =29

Approximately 6.89% of patients reported epigastric pain and 3.44% reported diarrhea as adverse event with Livwin treatment whereas 6.89% patients reported epigastric pain as adverse event with placebo treatment [Table 4].

Discussion

All the patients recruited in this study were of uncomplicated acute viral hepatitis. Both groups were comparable in age, sex and duration of illness. Mean age of patients in Livwin group was 29.93 ± 2.70 and that of placebo group was 33.37 ± 2.43. There were 22 male and 7 female patients in Livwin group and that in placebo group were 25 and 4, respectively [Table 1].

The polyherbal formulations like Liv.52,[5] Liv.52DS,[10] Hepax,[5] Kamalahar forte,[5] Arogyawardhini[5] and Valiliv[5] have got two or more similar contents as that of Livwin such as *Kutki, Arjuna, Daruharidra, Punarnava, Guduchi* and Bhumyamalaki, *Ashvagandha.* Therefore, the efficacy of these previous formulations was reviewed in the light of observation of present study. These polyherbal formulations have more components ranging from 9 to 19 and contain components other than herbal.[5] Livwin has seven components and all are herbal.

In the present study, there was significant earlier recovery of weakness in Livwin group as compared to placebo group [Table 2]

Baijal *et al,*[10] also observed that there was significant improvement of weakness in Liv.52 DS group over a period of 1 month.

Livwin contains *Ashwagandha* which is used as general tonic, useful in debility, fatigue, inability to concentrate specially due to the liver disease or other problems as stress.[11,12] Antioxidant action of Livwin probably can explain the mechanism for improvement of weakness. Mohanty *et al*, (1999)[13] found that *Ashwagandha* has optimum protective effect against selenite-induced oxidative damage lenses. Singh *et al,* (2000)[14] found antioxidant action of Kutki (*Picrorhiza kurroa*) in rats. Stanely *et al*, (2001)[15] observed that Guduchi (*Tinospora cordifolia)* root extract exhibited antioxidant action in rats.

Levels of serum bilirubin, AST and ALT were observed in normal range in significantly more number of patients earlier with Livwin treatment as compared to placebo [Table 3].

Dange *et al,*[5] observed that biochemical recovery (serum bilirubin, AST, ALT) occurred in significantly less days with *Arogyawardhini*, Hepax and Valiliv as compared to placebo. The results of present study are comparable with these studies.

Recovery of raised serum bilirubin with Livwin treatment is due to ingredients like *Kutki* and *Punarnava*, which helps in recovery of icterus and raised serum bilirubin by virtue of their choleretic action. Shukla *et al,*[16] observed choleretic action of *Kutki* in animal studies. Chandan *et al,*[17] in animal study observed choleretic action to *Punarnava*. Raised serum bilirubin in acute viral hepatitis presumably results from intrahepatic obstruction of biliary canaliculi; the obstruction is direct consequence of cellular inflammation. Begum *et al,*[18] observed anti-inflammatory action of *Ashwagandha*. Pandey *et al,*[19] observed anti-inflammatory action of *Kutki*.

Livwin contains *Bhuiamla*, which has activity against hepatitis B virus. In present study, number of hepatitis B positive patients were less (Livwin-1, placebo-1). Venkateswaren *et al,* (1987)[20] observed that *Bhuiamla* (*Phyllanthus niruri*) had antiviral action against Hepatitis B virus (HBV) *in vitro*. To prove the efficacy of Livwin in hepatitis B virus positive patients, further evaluation is needed.

Adverse events such as epigastric pain and diarrhea were reported by 10.37% patients in this study. Adverse events such as epigastric pain, diarrhea and skin rash were observed with Arogyawardhini in 10% patients, with Valiliv in 17.39% patients and with Liv.52 in 8.82% patients.[16] Adverse events observed with Livwin are comparable to adverse events with these polyherbal formulations.

The limitations of this study include the fact that viral markers for Hepatitis other than "B" was not done due to high cost of investigations.

Conclusions

Livwin caused significant earlier recovery of weakness in uncomplicated patients of acute viral hepatitis. Also Livwin caused earlier biochemical recovery as levels of serum bilirubin, AST and ALT were in normal range in significantly more number of patients at 2,4 and 8 weeks as compared to placebo. Adverse events reported with Livwin were epigastric pain and diarrhea. Hence, Livwin is effective in uncomplicated patients of acute viral hepatitis. Livwin needs further evaluation in treatment of hepatitis B virus infection.

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